Immunophenotypic and Pathologic Heterogeneity of Unclassified Renal Cell Carcinoma: A Study of 300 Cases

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Highlights

- Renal cell carcinoma, unclassified (RCC-U) is a diagnosis of exclusion.
- RCC-U is a morphologically and immunophenotypically heterogenous group of tumors.
- The diagnosis of RCC-U should be rendered after comprehensive work-up.

Abstract

Renal cell carcinoma, unclassified (RCC-U), is a heterogenous group of tumors that do not fit in any recognized histologic types. Immunohistochemical studies are frequently used to characterize these tumors. Herein, we sought to investigate the immunophenotypes of 300 cases of RCC-U. The cases were morphologically classified into three groups: oncocytoma/chromophobe renal cell carcinoma-like –Group 1; clear cell renal cell carcinoma-like – Group 2; and others (i.e., papillary renal cell carcinoma-like/collecting duct-like/pure sarcomatoid) – Group 3. Male-to-female ratio was 1.4. Most cases (168, 66%) were Group 1. Group 3 was associated with larger tumor size, advanced stage, and frequent lymph node metastases. The most commonly used immunohistochemical stains were CK7 (n=270; 89.5%), vimentin (n=186, 82%), CD10 (n=181; 59.9%), and AMACR (n=162; 54%). Pancytokeratin (79/101; 78.2%) and PAX8 (54/61; 88.5%) were diffusely positive in most cases, followed by AMACR (69/117; 59%). CD117 was positive in 53/118 cases (45%). RCC-U is a morphologically and immunophenotypically heterogenous group of tumors, comprehensive work-up is needed before rendering the diagnosis.

Introduction

The latest edition of the World Health Organization (WHO) classification on primary renal epithelial neoplasms include fourteen recognized and four provisional renal cell carcinoma (RCC) subtypes (1,2). Failure to classify an RCC, however, is not uncommon, seen in up to 5.7% of all RCCs, and "renal cell carcinoma, unclassified (RCC-U)" designation is used for such tumors (3). In the 2016 WHO classification system, "renal cell carcinoma, unclassified (RCC-U)" designation is used for tumors that do not fit in any recognized histologic types (4). These tumors include those with a combination of features of more than one recognized subtype, with mucin production, or with unrecognized epithelial cell subtypes; low or high grade unclassified oncocytic neoplasms (4). RCC-U may have pure sarcomatoid morphology with unrecognized epithelial cell type or without an identifiable epithelial component (4). In a recent study, Perrino and colleagues further subclassified RCC-U into three morphological subgroups based on predominant morphological features: oncocytoma/chromophobe RCC-like – Group 1; clear cell RCC-like – Group 2; and others (i.e., papillary RCC-like/collecting duct-like/pure sarcomatoid) – Group 3 (5).

RCC-U is a heterogenous group of tumors with different cytology, genetics, microenvironment, growth pattern and metastatic potential. Its clinical outcome is variable, and is mainly determined by histologic grade and pathologic stage (5). Ancillary studies are virtually always employed in the diagnostic work-up of RCC-U, and immunohistochemistry (IHC) is the most utilized tool. Practical recommendations from various genitourinary pathology experts on the use of IHC are targeted in light of whether the tumor is predominantly eosinophilic (6-9) , clear cell (7-10), or low- or high- grade cytology (6,7) or different growth patterns (7,9);

however, immune-profile of RCC-U has not been systematically evaluated. Herein, we sought to investigate the immunophenotypes of RCC-U in this largest series reported to date.

Materials and Methods

Three hundred cases diagnosed as RCC-U at the Indiana University between 2006-2019 were analyzed. The RCC-U cases (n=130) reported by Perrino et al (5) were also included. Available hematoxylin and eosin stained slides and immunohistochemical (IHC) studies were reviewed by the authors (MA and LC) using the 2016 WHO classification criteria (4). Type of the procedure (partial/total nephrectomy or biopsy), gender, age at diagnosis, cytomorphological features, tumor grade and pathologic stage were recorded (11-13). As previously described by Perrino et al (5), the cases were classified into three groups based on their predominant morphologic feature: oncocytoma/chromophobe RCC-like –Group 1; clear cell RCC-like – Group 2; and others (i.e., papillary RCC-like/collecting duct-like/pure sarcomatoid) – Group 3. The predominant morphological features of each case were designated after review the slides by the authors (MA and LC).

Seventeen of the most used biomarkers for each case, when applicable, were recorded. These antibodies included AE1/AE3 (AE1/AE3 clone, ready-to-use [RTU], Dako), carbonic anhydrase IX (CAIX; MRQ-54 clone, 1:200, Cell Marque), cathepsin K (3F9 clone, 1:100, Abcam), CD10 (56C6 clone, RTU, Dako), cytokeratin 7 (CK7; OV-TL 12/30, Dako), CK20 (Ks20.8 clone, RTU, Dako), CD117 (YR145 clone, RTU, Cell Marque), epithelial membrane antigen (EMA; E29 clone, RTU, Dako), fumarate hydratase (FH; J-13 clone, 1:200, Santa Cruz), HMB45 (HMB45, RTU, Dako), melan A (A103 clone, RTU, Dako), P504S (13H4 clone, RTU, Dako), PAX8 (MRQ-50 clone, 1:100, Cell Marque), succinate dehydrogenase B (SDHB;

21A11AE7 clone, 1:500, Abcam), TFE3 (MRQ-37, 354R-18 clone, 1:100, Cell Marque), and vimentin (V9 clone, RTU, Dako). The special stain, colloidal iron, was interpreted as "atypical" where there was expression in unexpected areas of the tumor cells, such as luminal-only staining.

This research was approved by the Institutional Review Board at Indiana University.

Results

A total of 300 cases were reviewed. The male-to-female ratio was 1.4 (179/121) and the patients ranged in age from 19–88 years (median, 61 years). Of these cases, 180 (60%) were from total nephrectomies, 118 (39%) from partial nephrectomies, and 2 from renal core needle biopsies. Most of the RCC-U cases (168, 66%) were Group 1, whereas Groups 2 and 3 had 52 (17%) and 50 (16%) cases, respectively (**Figure 1A-1H**). Median tumor size was 5.0 cm (1–24.9 cm). World Health Organization/International Society of Urologic Pathology (WHO/ISUP) nuclear grade 3 was the most common (137, 46%), followed by grade 2 (96, 32%), and grade 4 (57, 19%). Sarcomatoid features were seen in 19 cases, most of which were in Group 3 (accounting for 20% of all cases in this group). Most of the cases in Groups 1 and 2 were organ confined (70% and 54%, respectively). In contrast, 62% of cases in Group 3 had at least pT3 disease. Most cases did not have information about lymph node status, although 55% (12/22) of the cases with known lymph node status in Group 3 had at least one metastatic lymph node. (**Table 1**).

Overall biomarker profile for each group is illustrated in **Tables 2 and 3** and **Figure 2**. The most commonly used immunohistochemical stains were CK7 (n=270; 89.5%), vimentin (n=186, 82%), CD10 (n=181; 59.9%), and AMACR (n=162; 54%). Pancytokeratin (79/101;

78.2%) and PAX8 (54/67; 88.5%) were diffusely positive in most cases, followed by AMACR (69/117; 59%). CD117 was positive in substantial amount of cases (53/118; 45%). Colloidal iron was diffusely positive in (24/107; 22%), although atypical expression was not uncommon (20/107;18%).

In group 1 RCC-U, CK7 was positive in majority of cases (109/183; 59%), focal expression (57/109;52%) was as common as diffuse expression (52/109;48%) (**Figure 2, Table 2)**. Approximately half of the cases in group 1 RCC-U (50/99;51%) had CD117 expression, in a predominantly diffuse (40/50;80%) pattern. AMACR expression was seen in majority of group 1 cases (47/72; 65%). Colloidal iron staining was observed in many cases in this group (43/99;43% of cases), roughly in half of the cases the staining pattern was atypical (20/43;46%). In group 2 (**Figure 2c**), most tumors had CAIX (30/37; 81%), 28 diffuse), CD10 (38/41; 92%), and AMACR (27/34; 79%) with mostly diffuse pattern (CAIX 28/30; 93%, CD10 32/38; 84%, AMACR 24/27;88%). CK7 was also positive in more than half of the cases (24/46 52%), mostly frequently with diffuse pattern (15/24;62%). Similarly, the majority of tumors in group 3 RCC-U (**Figure 2d**) had CAIX (11/22 77%), CD10 (24/29 82%), and AMACR (28/32 87%) expressions with mostly diffuse pattern (CAIX 11/11; 100%, CD10 18/24; 66%, AMACR 24/28; 86%). Few cases in group 3 had CK7 expression (15/41; 36%) with mainly focal expression (9/15; 60%). (**Figure 2, Table 2)**.

TFE3 was expressed by immunohistochemistry in few cases (9/102; 8%) (**Figure 3a**), although all cases had subsequent negative TFE3 findings by fluorescence in situ hybridization. Sixteen cases (~5%) had features of "low-grade oncocytic tumor" including bland eosinophilic nuclei, areas of small distinct and confluent tumor clusters, and diffuse CK7 expression with negative CD117 (**Figure 3b**). Three of 198 (~2%) eosinophilic tumors had high nuclear grade,

intermixed clear cells with intracytoplasmic vacuoles, and diffuse cathepsin K expression, consistent with "high-grade oncocytic tumor" (**Figure 3c**). In Group 1, five cases had CK20 expression, although these tumors did not have morphologic evidence of eosinophilic solid and cystic RCC (**Figure 3d**).

Discussion

The current cohort of three hundred cases of unclassified renal cell carcinoma (RCC-U), to the best of our knowledge, is the largest series ever reported in the English literature. One of our main goals is to document epidemiologic characteristics of the patients, histologic grade and staging information of these tumors, as well as analyzing the immunohistochemical characteristics of each morphological subgroups. This report of comprehensive immunoprofiles of the largest RCC-U series may serve as a main reference for future studies of this uncommon disease.

Many RCC subtypes share multiple overlapping morphologic and immunophenotypic features (**Figures 4** and **5)**, and a panel of biomarkers are often required to finalize diagnostic workup (2,7,9,14-16). Diverse morphological manifestations of RCC-U have been observed in current and previous RCC studies (3,5,17-24) The majority of RCC-U with eosinophilic morphology (Group 1) had less advanced disease when compared to RCC-U with high-grade features (Group 3). Eosinophilic renal tumors pose a diagnostic challenge because oncocytoma, a benign neoplasm, is in the differential. The most commonly used immunohistochemical markers for oncocytoma are reported to be CK7 (94%), CD117 (71%), and vimentin (65%), as well as the special stain, colloidal iron (59%) (25); these are also the most common biomarkers (and special stain) in the diagnostic workup of Group 1 RCC-U in our study (**Figure 2, Table 3**).

Clear cell histology is also commonly observed in RCC-U (designated Group 2 RCC-U, **Table 3**) (5). The majority of group 2 RCC-U cases had diffuse CAIX and CD10 expression, and AMACR expression was also present in 79% of cases. AMACR expression might be helpful in differentiating RCCU from clear cell renal cell carcinoma, as its expression is seen only up to 25% of cases with usually focal pattern (7,9). Prominent morphologic variation, including true papillary growth, was present in these tumors. Important differential diagnostic considerations include clear cell papillary RCC and MIT-family translocation associated RCC (MIT-RCC) (**Figure 4**) (14).

Group 3 RCC-U includes tumors with predominantly papillary RCC-like or collecting duct-like phenotype and tumors with pure sarcomatoid morphology (5). Group 3 RCC-U was associated with larger tumor size, advanced stage, and frequent lymph node metastases. Diagnosis of RCC with poorly differentiated morphologic features should start with ruling out tumors of urothelial or secondary origin (14). Clinical history and expression profile of SMARCB1 and OCT4 may help identify renal medullary carcinoma (loss of SMARCB1/positive OCT4) and collecting duct carcinoma (retained SMARCB1/negative OCT4) (7). dFH-RCC should also be in the differential as the characteristic prominent inclusion-like nucleoli may not be readily seen. ALK-RCC have high-grade morphology that is similar to renal medullary carcinoma with no history of hemoglobinopathy, and is rare—like these two entities—as only 2/88 RCC were found to have ALK-IHC expression (26). Pure sarcomatoid morphology is now considered one of the definitions of RCC-U (4), therefore adequate sampling of the tumor is required (19).

In summary, RCC-U constitutes a group of distinct renal neoplasms with substantial immunophenotypic and morphologic heterogeneity. RCC-U, by its nature, is a diagnosis of

exclusion and efforts in identifying certain immunoprofile specific for RCC-U cases are fraught with difficulties. Nonetheless, interpreting the immunoprofile in light of the morphologic subgroups may help in distinguishing RCC-U from recognized entities. The diagnosis of RCC-U should be rendered after thorough evaluation of morphologic and immunohistochemical biomarker features.

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Figure Legends

Figure 1. Morphologic and immunohistochemical staining features of selected cases in each group. Group 1 RCC-U are cases with oncocytoma/chromophobe RCC-like morphology, although many features corresponding to more than one entity can be seen with abrupt changes. Psammoma bodies (**arrow**) are also not specific to any renal tumors (**A, 40x**). This eosinophilic neoplasm shows complete loss of CK7 expression (**B, 100x**) with internal positive control of normal renal tubules. Atypical colloidal iron staining (**C, 200x**) is seen where smaller eosinophilic tumor cells have strong membranous/cytoplasmic staining, whereas larger cells are negative. Group 2 RCC-U may have morphologic features that are acceptable to clear cell RCC (**D, 100x**), although in this case CAIX expression is completely lost (**E, 100x**), with oncocytoma-like CK7 expression (**F, 100x**). Group 3 RCC-U are usually high grade (**G, 100x**), therefore PAX8 (**H, 100x**) and p63 (**I, 100x**) expressions should be evaluated to determine the renal origin.

Figure 2. Summary of immunohistochemical stains performed in all cases (**A**), in Group 1 (**B**), in Group 2 (**C**), and in Group 3 (**D**).

Figure 3. RCC-U cases resembling recognized or emerging entities. An eosinophilic tumor with high-grade nuclear features and solid to packed tubular growth pattern (**A, 100x**) shows diffuse and strong TFE3 expression (**B, 100x**), although AE1/AE3 is strongly expressed (**C, 100x**) and TFE3-FISH was negative in this case. Some eosinophilic RCC-U (**D**, **100x**) have focal CK20 expression (**E, 100x**), with CK7 absence (**F, 100x**) resembling eosinophilic solid and cystic RCC, although morphologic features, such as cystic growth or coarse intracytoplasmic granules, are absent. A recently identified entity, low-grade oncocytic tumor, has nuclear features similar

to oncocytoma with solid growth pattern with abrupt edematous changes in the stroma and fused tumor nests of varying size (**G, 100x**). Contrary to oncocytoma, these tumors are characterized by diffuse CK7 expression (**H, 100x**) and negative **CD117** (I). Finally, high-grade oncocytic tumors (**J, 100x**) have diffuse cathepsin K expression (**K, 100x**), no loss of pancytokeratin (**L, 100x**), and negative TFE3 expression (not shown).

Figure 4. Immunophenotypic and morphologic heterogeneity of RCC. With an increasing number of new entities, diagnosing renal cell neoplasms is challenging. Several morphologic features, including cytoplasmic features, growth pattern, and nuclear features, should be taken into account, although many entities have overlapping features. Abbreviations: ACKD-RCC = acquired cystic kidney disease-associated renal cell carcinoma, ALK-RCC = anaplastic lymphoma kinase-associated renal cell carcinoma, AMLEC = angiomyolipoma with epithelial cysts, BSPRCC = biphasic solid and cystic renal cell carcinoma, CCRCC = clear cell renal cell carcinoma, CDC = collecting duct carcinoma, ChRCC = chromophobe renal cell carcinoma, dFHRCC = fumarate hydratase-deficient renal cell carcinoma, dSDH-RCC = succinate dehydrogenase-deficient renal cell carcinoma, eCCRCC = epithelioid clear cell renal cell carcinoma, eChRCC= epithelioid chromophobe renal cell carcinoma, ESC-RCC = eosinophilic solid and cystic renal cell carcinoma, HOT = high-grade oncocytic tumor, LOT = low-grade oncocytic tumor, MCRNLMP = multilocular clear cell renal neoplasm with low malignant potential, MIT-RCC = MIT-family translocation associated renal cell carcinoma, MTSCC = mucinous tubular and spindle cell carcinoma, PA = papillary adenoma, PRCC = papillary renal cell carcinoma, RAT = renal cell carcinoma with angioleiomyomatous stroma, RMC = renal

medullary carcinoma, TcRCC = tubulocystic renal cell carcinoma, TFRCC = thyroid follicle like renal cell carcinoma.

Figure 5: After determining that the tumor cells are predominantly eosinophilic (**A**), clear (**B**), or with high-grade features (**C**), immunohistochemistry should be performed if morphologic evaluation is insufficient for diagnosis. Despite classical definition, MIT-RCC can have many different growth patterns. Color codes on different entities match with the color of prominent growth pattern. Abbreviations: ACKD-RCC = acquired cystic kidney disease-associated renal cell carcinoma, ALK-RCC = anaplastic lymphoma kinase-associated renal cell carcinoma, AMLEC = angiomyolipoma with epithelial cysts, BSPRCC = biphasic solid and cystic renal cell carcinoma, CCRCC = clear cell renal cell carcinoma, CDC = collecting duct carcinoma, ChRCC = chromophobe renal cell carcinoma, dFHRCC = fumarate hydratase-deficient renal cell carcinoma, dSDH-RCC = succinate dehydrogenase-deficient renal cell carcinoma, eCCRCC = epithelioid clear cell renal cell carcinoma, eChRCC= epithelioid chromophobe renal cell carcinoma, ESC-RCC = eosinophilic solid and cystic renal cell carcinoma, HOT = high-grade oncocytic tumor, LOT = low-grade oncocytic tumor, MCRNLMP = multilocular clear cell renal neoplasm with low malignant potential, MIT-RCC = MIT-family translocation associated renal cell carcinoma, MTSCC = mucinous tubular and spindle cell carcinoma, PA = papillary adenoma, PRCC = papillary renal cell carcinoma, RAT = renal cell carcinoma with angioleiomyomatous stroma, RMC = renal medullary carcinoma, TcRCC = tubulocystic renal cell carcinoma, TFRCC = thyroid follicle like renal cell carcinoma.

Table 1. Characteristic features of the study cohort.

	All categories	Oncocytoma/ChRCC-like	Clear cell RCC-like	PRCC-like/CDC-like/pure sarcomatoid
Total case (%)	300 (100%)	198 (66%)	52 (18%)	50 (16%)
Median age (range)	61 (19 -88)	62 (19-88)	59 (33 – 85)	
Male/female (ratio)	179/121 (1.4)	116/82 (1.4)	30/22 (1.3)	
Procedure				
Radical nephrectomy	180 (60%)	106 (54%)	32 (62)	42 (84%)
Partial nephrectomy	118 (39%)	90 (45%)	20 (38)	8 (16%)
Biopsy	2 (1%)	2 (1%)	0	0
Median tumor size (range) (cm)	5 (1-24.9)	4.5 (1-23.5)	4.8 (1.4-14.7)	6.5 (2-24.9)
Nuclear grade (%)				
NA	10 (3%)	5 (2.5)	4 (8%)	1 (2%)
1	0	0	0	0
2	96 (32%)	77 (38%)	13 (25%)	6 (12%)
3	137 (46%)	87 (44%)	27 (52%)	23 (46%)
4	57 (19%)	29 (15%)	8 (15%)	20 (40%)
Sarcomatoid component	19 (6%)	7 (4%)	2 (4%)	10 (20%)
Tumor stage				
T1a	112 (38%)	83 (42%)	19 (37%)	10 (20%)

T1b	45 (15%)	32 (16%)	6 (12%)	7 (14%)
T2a	12 (4%)	9 (5%)	2 (4%)	1 (2%)
T2b	14 (5%)	11 (6%)	2 (4%)	1 (2%)
T3a	98 (33%)	54 (27%)	23 (46%)	21 (42%)
T3b	4 (1%)	2 (1%)	0	2 (4%)
T3c	3 (1%)	1 (<1%)	0	2 (4%)
T4	10 (3%)	4 (2%)	0	6 (12%)
Lymph node status				
Not applicable	230 (77%)	158 (81%)	44 (85%)	28 (56%)
N0	42 (14%)	26 (13%)	6 (12%)	10 (20%)
N1	26 (9%)	12 (6%)	2 (4%)	12 (24%)

Footnote: Staging is per American Joint Committee on Cancer cancer staging manual, 8th edition. CDC= collecting duct carcinoma; ChRCC = chromophobe renal cell carcinoma; PRCC = papillary renal cell carcinoma; RCC = renal cell carcinoma.

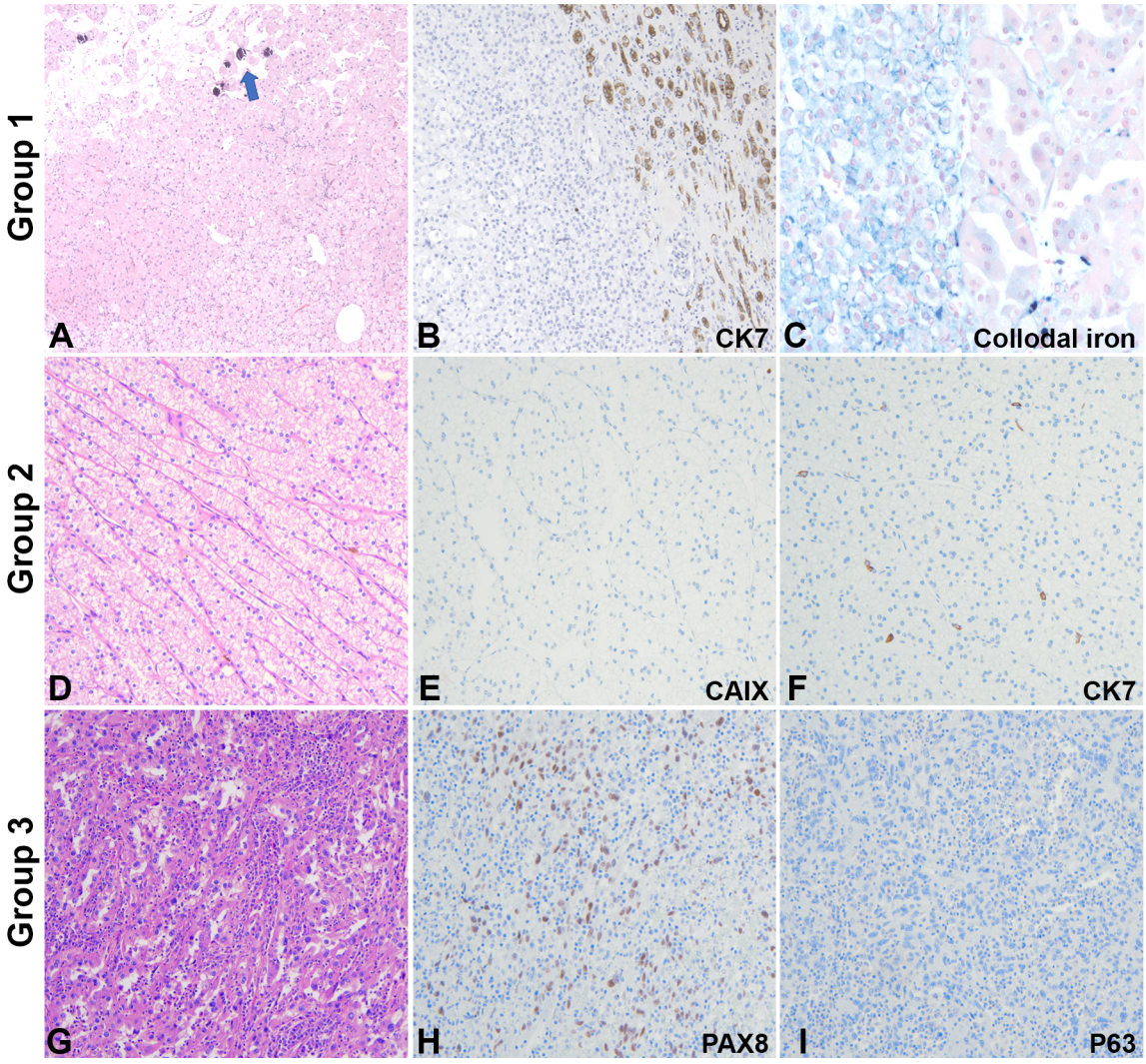
Table 2. Immunohistochemical summary of 300 renal cell carcinoma, unclassified cases.

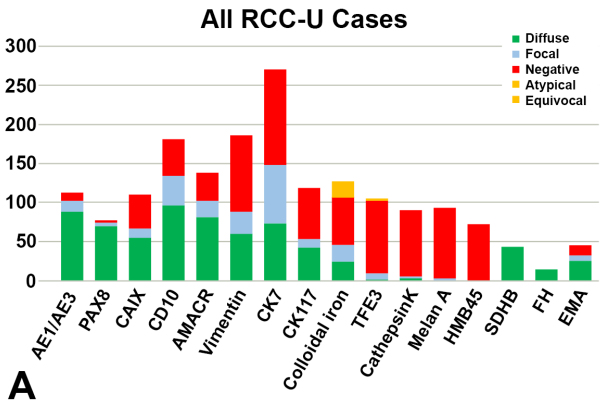
	Pancytokeratin	PAX8	CAIX	CD10	AMACR	Vimentin	CK7	CD117	Colloidal iron	TFE3	Cathepsin K	MelanA	HMB45	FH	SDHB	EMA	TFE3 FISH
Total performed	112	77	110	181	162	186	270	118	107	102	90	93	72	15	44	45	10
Diffuse	88	70	55	96	81	60	73	42	24	1	3	0	0	0	0	25	
Focal	14	4	11	38	21	28	75	11	22	8	2	3	0	0	0	7	
Negative	10	3	44	47	36	98	122	65	61	93	85	90	72	15	44	13	10
Equivocal										3							
Atypical									20								

Footnote: Diffuse = expression in more than 50% of tumor cells; focal =expression in less than 50% of tumor cells; negative = no expression; equivocal = weak and/or focal/partial staining; atypical = positive staining with unusual patterns, e.g. luminal only stain.

Table 3. Morphologic and Immunophenotypic differences in renal cell carcinoma, unclassified (RCCU)

Morphologic grouping	Morphologic features	Tumor characteristics	Biomarker expression (% positive)
Group 1: Oncocytoma/Chromophobe RCC-like (Group 1)	Predominantly eosinophilic cytoplasm, nested and/or solid sheets with occasional papillae formation	• 198/300 (66%) • Mostly organ confined (70%) • Relatively small (median 4.5 cm), • Few ISUP/WHO grade 4 (15%)	CK7 (59%), CD117 (50%), AMACR (65%), vimentin (39%), colloidal iron (43%)
Group 2: Clear cell RCC-like	Predominantly clear cytoplasm and delicate vasculature with occasional papillae formation	• Majority organ confined (54%) • Few ISUP/WHO grade 4 (15%)	CAIX (81%), CD10 (92%), AMACR (79%), CK7 (52%)
Group 3: Papillary RCC-like/Collecting Duct carcinoma-like/Pure sarcomatoid	Tumors with fine fibrovascular cores/tubulopapillary architecture and high nuclear grade	• Large tumors (median 6.5 cm) • Advanced tumor stage (≥T3a 62%), • ISUP/WHO grade 4 (40%)	CAIX (77%), CD10 (82%), AMACR (87%), CK7 (36%)


Group 1
Group 2
Group 3
A
B
CK7
C
Collodal iron
D
E
CAIX
F
CK7
G
H
PAX8
I
P63


All RCC-U Cases
Diffuse
Focal
Negative
Atypical
Equivocal
300
250
200
150
100
50
0
AE1/AE3
PAX8
CAIX
CD10
AMACR
Vimentin
CK7
CK117
Colloidal iron
TFE3
CathepsinK
Melan A
HMB45
SDHB
FH
EMA

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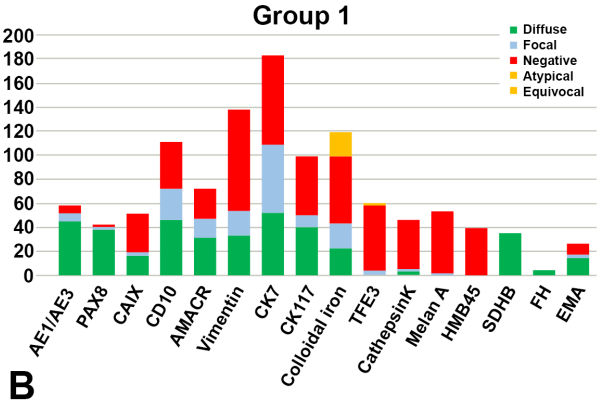
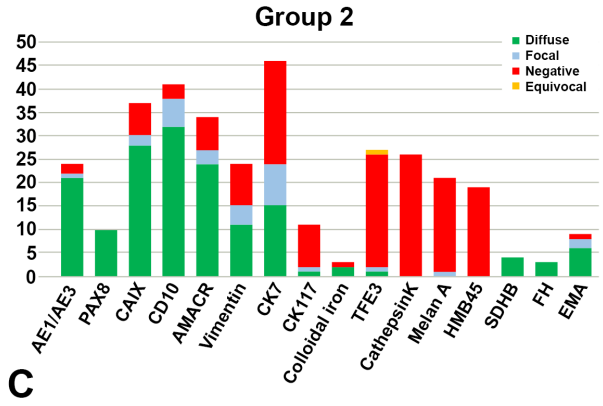
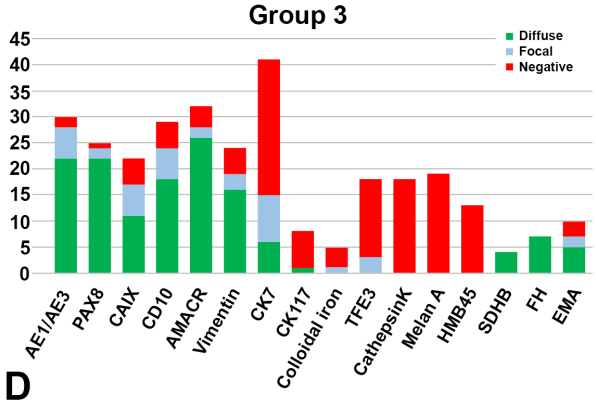

Group 1
Diffuse
Focal
Negative
Atypical
Equivocal
200
180
160
140
120
100
80
60
40
20
0
AE1/AE3
PAX8
CAIX
CD10
AMACR
Vimentin
CK7
CK117
Colloidal iron
TFE3
CathepsinK
Melan A
HMB45
SDHB
FH
EMA

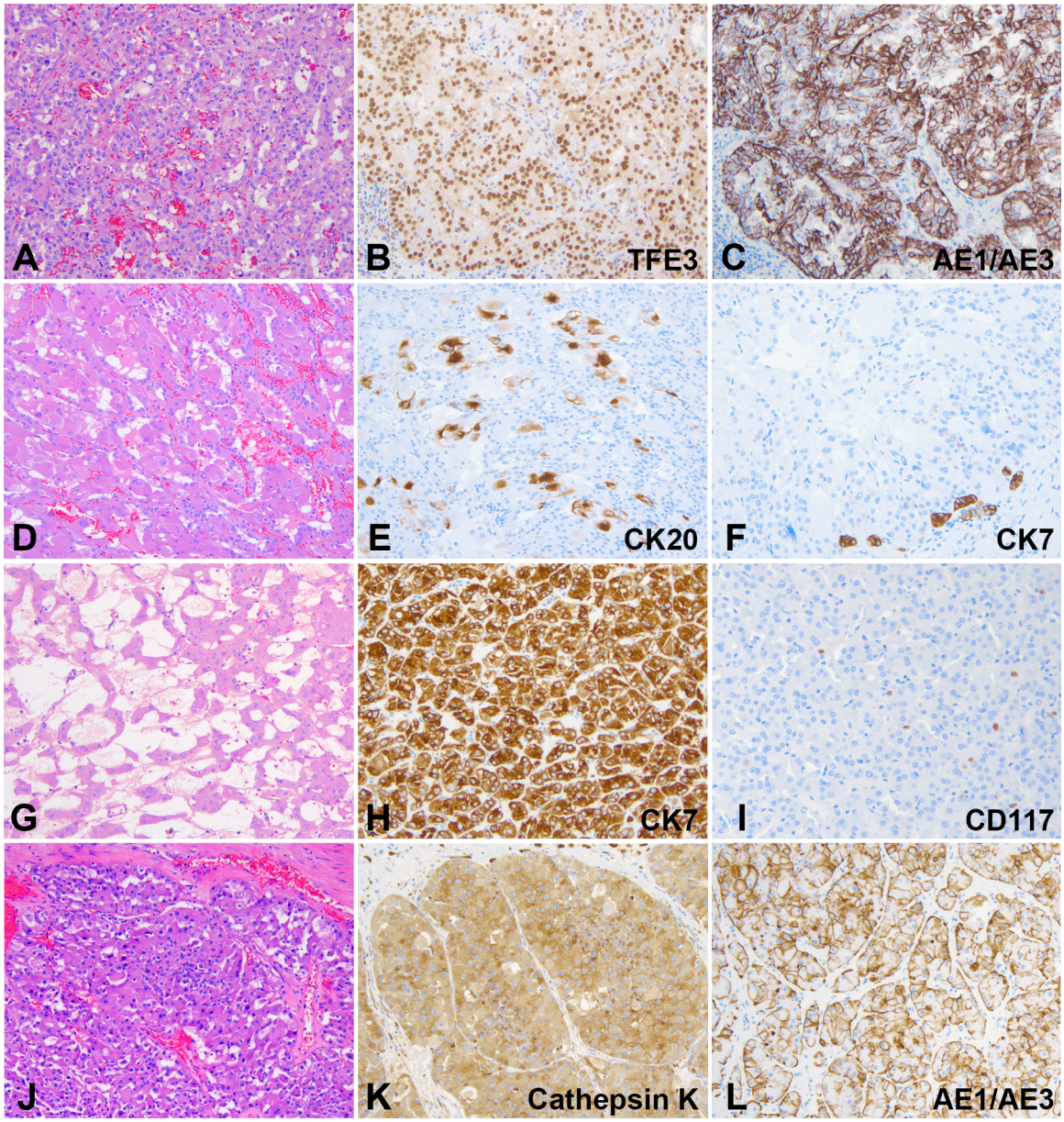
B

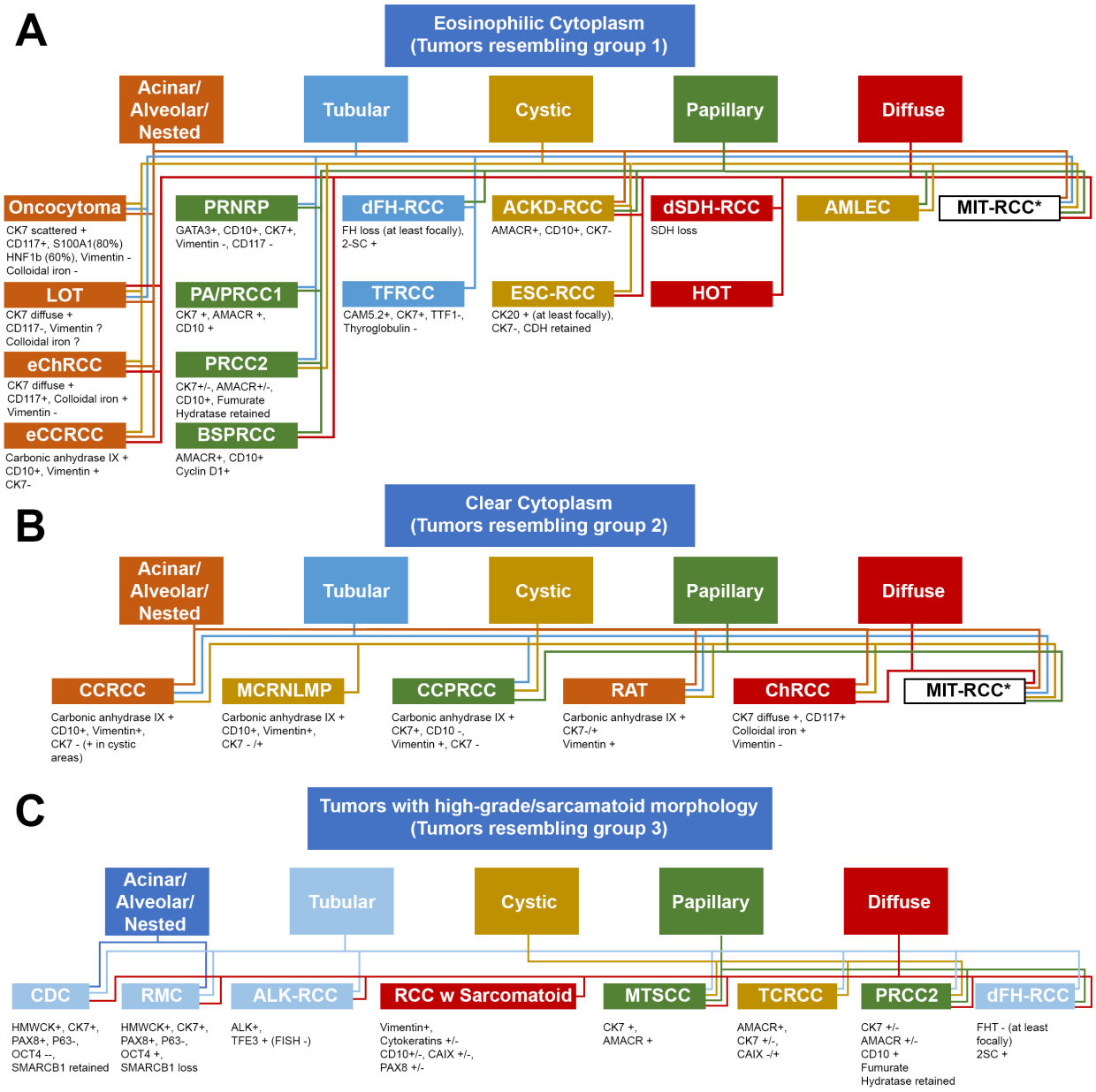

Group 2
Diffuse
Focal
Negative
Equivocal
50
45
40
35
30
25
20
15
10
5
0
AE1/AE3
PAX8
CAIX
CD10
AMACR
Vimentin
CK7
CK117
Colloidal iron
TFE3
CathepsinK
Melan A
HMB45
SDHB
FH
EMA

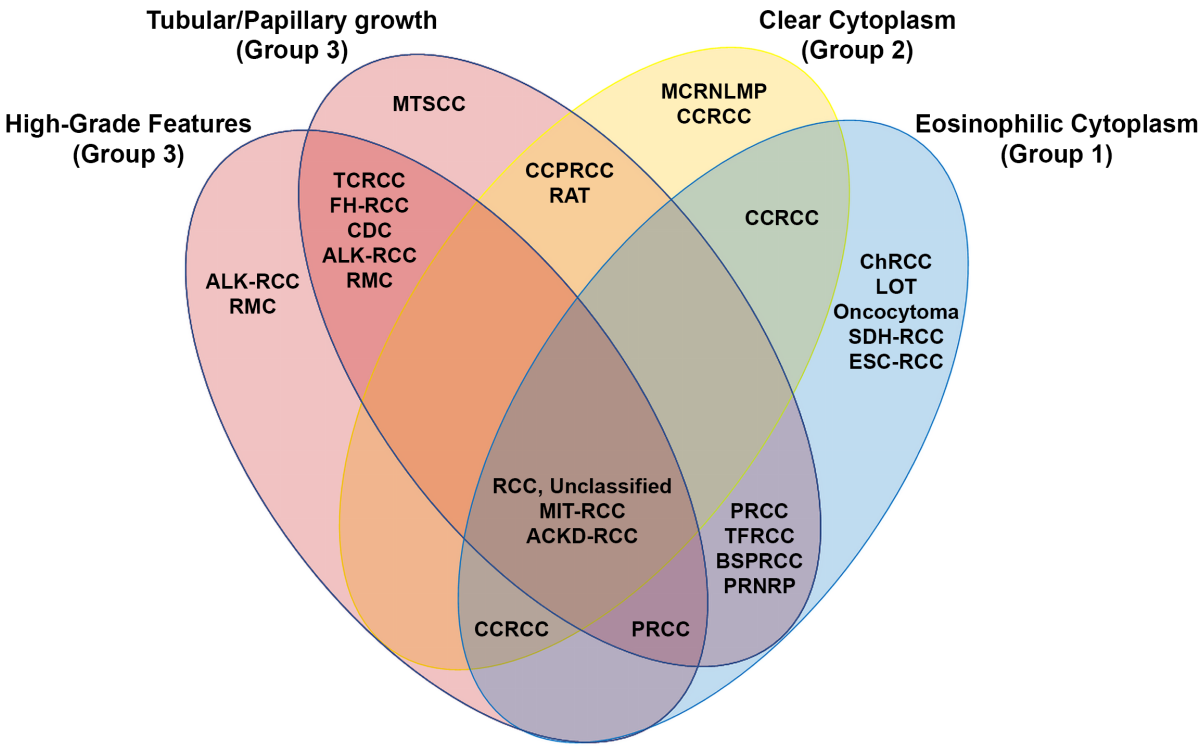
C


Group 3
Diffuse
Focal
Negative
45
40
35
30
25
20
15
10
5
0
AE1/AE3
PAX8
CAIX
CD10
AMACR
Vimentin
CK7
CK117
Colloidal iron
TFE3
CathepsinK
Melan A
HMB45
SDHB
FH
EMA

D


A
B
TFE3
C
AE1/AE3
D
E
CK20
F
CK7
G
H
CK7
I
CD117
J
K
Cathepsin K
L
AE1/AE3


A
Eosinophilic Cytoplasm
(Tumors resembling group 1)
Acinar/
Alveolar/
Nested
Tubular
Cystic
Papillary
Diffuse
Oncocytoma
CK7 scattered +
CD117+, S100A1(80%)
HNF1b (60%), Vimentin -
Colloidal iron -
PRNRP
GATA3+, CD10+, CK7+,
Vimentin -, CD117 -
dFH-RCC
FH loss (at least focally),
2-SC +
ACKD-RCC
AMACR+, CD10+, CK7-
dSDH-RCC
SDH loss
AMLEC
MIT-RCC*
LOT
CK7 diffuse +
CD117-, Vimentin ?
Colloidal iron ?
PA/PRCC1
CK7 +, AMACR +,
CD10 +
TFRCC
CAM5.2+, CK7+, TTF1-,
Thyroglobulin -
ESC-RCC
CK20 + (at least focally),
CK7-, CDH retained
HOT
eChRCC
CK7 diffuse +
CD117+, Colloidal iron +
Vimentin -
PRCC2
CK7+/-, AMACR+/-,
CD10+, Fumurate
Hydratase retained
eCCRCC
Carbonic anhydrase IX +
CD10+, Vimentin +
CK7-
BSPRCC
AMACR+, CD10+
Cyclin D1+
B
Clear Cytoplasm
(Tumors resembling group 2)
Acinar/
Alveolar/
Nested
Tubular
Cystic
Papillary
Diffuse
CCRCC
Carbonic anhydrase IX +
CD10+, Vimentin+,
CK7 - (+ in cystic
areas)
MCRNLMP
Carbonic anhydrase IX +
CD10+, Vimentin+,
CK7 - /+
CCPRCC
Carbonic anhydrase IX +
CK7+, CD10 -,
Vimentin +, CK7 -
RAT
Carbonic anhydrase IX +
CK7-/+
Vimentin +
ChRCC
CK7 diffuse +, CD117+
Colloidal iron +
Vimentin -
MIT-RCC*
C
Tumors with high-grade/sarcamatoid morphology
(Tumors resembling group 3)
Acinar/
Alveolar/
Nested
Tubular
Cystic
Papillary
Diffuse
CDC
HMWCK+, CK7+,
PAX8+, P63-,
OCT4 –,
SMARCB1 retained
RMC
HMWCK+, CK7+,
PAX8+, P63-,
OCT4 +,
SMARCB1 loss
ALK-RCC
ALK+,
TFE3 + (FISH -)
RCC w Sarcomatoid
Vimentin+,
Cytokeratins +/-
CD10+/-, CAIX +/-,
PAX8 +/-
MTSCC
CK7 +,
AMACR +
TCRCC
AMACR+,
CK7 +/-,
CAIX -/+
PRCC2
CK7 +/-
AMACR +/-
CD10 +
Fumurate
Hydratase retained
dFH-RCC
FHT - (at least
focally)
2SC +


Tubular/Papillary growth
(Group 3)
Clear Cytoplasm
(Group 2)
High-Grade Features
(Group 3)
Eosinophilic Cytoplasm
(Group 1)
MTSCC
MCRNLMP
CCRCC
TCRCC
FH-RCC
CDC
ALK-RCC
RMC
CCPRCC
RAT
CCRCC
ALK-RCC
RMC
ChRCC
LOT
Oncocytoma
SDH-RCC
ESC-RCC
RCC, Unclassified
MIT-RCC
ACKD-RCC
PRCC
TFRCC
BSPRCC
PRNRP
CCRCC
PRCC